## REMARKS

Claims 245-251, 253-255 and 257-265 are pending in the above-referenced application. Claims 245, 247, 248 and 306 have been amended to more distinctly claim that which Applicants regard as the invention and to advance prosecution. Amended claim 245 is supported by the specification in Figures 15-18 and in Examples 12-15 and pages 59-61. Amended Claim 247 supported by the specification on pages 52-53, page 65, lines 9-20 (bottom of the page), Figure 15 and example 12. Claim 248 has been amended to recite that the entity further comprises a binder. Claim 306 has been amended to incorporate amendments to claim 247. No new matter has been added to any of the amended claims. Furthermore, claims 249-250, 252, 254-260 and 266-305 have been canceled. Applicants reserve the right to file subsequent continuation and/or divisional applications containing claims encompassing the canceled subject matter.

Applicants further note that claim 307 has been added to recite a specific embodiment, a method of introducing a nucleic acid component into a cell using the construct recited in claim 245. New claim 307 is supported by the specification.

### 1. The Rejection Under 35 USC §112, First Paragraph (Written Description)

Claims 245-255, 257-265, and 306 have been rejected under 35 U.S.C. §112, first paragraph (written description). The Office Action specifically states:

> Contrary to Applicant's assertions, one of skill in the art would not be able to readily recognize the genus of species encompassed by the claims based merely on the schematic drawings, which do not clearly demonstrate adequate description of the entire genus of species encompassed by the claims. As previously indicated, the specification as filed does not adequately describe a representative number of species of the claimed invention unless one of skill in the art would be able to envisage the structure, in this case the chemical structure (nucleic acid, protein, and

> other claimed chemical compositions, including the cells), of the claimed invention. Since none of the examples, either prophetic or exemplified by reduction to practice, in the specification as filed provide a clear description of the genus and species within the genus of the claimed invention, one of skill in the art would not have recognized that application was in possession of a representative number of species of the claimed invention at the time the invention was made.

The Office Action further states

> Applicants contend that a detailed description of the compositions of the present invention is provided on pages 48-59, particularly pages 50-55. The terms "nucleic acid component", "domain", and "binder" are clearly defined on pages 48-49, and various examples of useful domains are described. Examples of various antibodies are provided in the paragraph bridging 53 and 54. These include useful domains with nonspecific cell binding properties (see page 53), useful domains with specific cell binding properties (see page 53), useful domains with specific nucleic acid component binding properties (see page 54). Applicants also assert that the specification describes specific embodiments. Contrary to Applicant's assertions, the embodiments disclosed in the instant specification are not specific, as they only provide general guidance as to what broad types of compositions are instantly claimed. The descriptions in both the specification and in the figures do not provide an adequate description of specific species, nor representative number of such species, of compositions which may be envisioned to produce a product in a cell as claimed.

Applicants respectfully traverse the rejection. First, Applicants note that claims 245 and 247 have been amended to more distinctly recite the subject matter of the invention. Specifically, claim 245 has been amended to clearly denote that the construct is used as a template for nucleic acid synthesis, added language that more clearly defines the nature of the connection between the construct and lastly that the nucleic acid linker that binds the nucleic acid construct to the antibody is a covalent linkage. The use of all of these elements

is described in the specification and explicit examples containing all of these elements are clearly shown in Figures 15, 16, 17 and 18. Thus an adequate description of claim 245 has been provided.

Applicants further note that claims 247 and 306 have been amended to recite specific binding domains for nucleic acids (a linear nucleic acid complementary to a sequence of the specific nucleic acid component or a protein that binds to a ligand of a modified nucleotide in the specific nucleic acid component) and specific binding domains for a cell of interest (a hormone specific to a receptor on said cell of interest, a lectin specific for a sugar on the surface of said cell of interest, a virus particle or viral fragment that binds to a receptor on the surface of said cell of interest and an antibody that recognizes an epitope on the surface of said cell). A specific nucleic acid component is defined as a nucleic acid construct that directs synthesis of a nucleic acid product, wherein said nucleic acid component comprises a nucleic acid sequence desired to be delivered to said cell.

Applicants note that the MPEP § states that written description requirement of 35 USC §112, first paragraph can be met by

> Show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics…i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Applicants assert that sufficient identifying characteristics were provided in the disclosure with respect to claims 245 and 247. Applicants note that the claimed construct in claim 245 and the claimed composition in claim 247 are actually schematically depicted in Figures 15-18. Applicants further note that structure is not required for an adequate description of a biological macromolecule. This was articulated by the CAFC in *Faulkner v, Inglis*, 448 F .3d 1357 (Fed Cir. 2006). The Court enunciated the following description principles: (1) examples are not necessary to support the adequacy of a written description, (2) the written description standard may be met even where actual reduction to practice of an

invention is absent, and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

Applicants note that claim 246 depends from claim 245 and claims 248-253, 261-262 depend ultimately from claim 247. Therefore, arguments made with respect to claims 245 and 247 would apply to these claims as well. Claims 254-255 and 257-260 have been canceled.

In view of the above arguments and amendments, Applicants assert that the rejections under 35 USC §112, first paragraph (written description) have been overcome. Therefore, Applicants respectfully request that the rejections under 35 USC §112, first paragraph (written description) be withdrawn.

**2. The Rejections Under 35 USC 112, First Paragraph (Enablement)**

Claims 263-265 have been rejected under 35 U.S.C. §112, first paragraph, lack of enablement. It is asserted that the claim while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (in vitro), does not reasonably provide enablement for methods of expressing a nucleic acid product in a whole organism (in vivo). The Office Action specifically states:

> Applicant's arguments filed 8-24-08 have been fully considered but they are not persuasive. Applicant argues that the entire scope of the instant invention was fully enabled at the time of filing, and that various domains with specific cell binding properties are disclosed in the specification. Applicant also submitted several references that illustrate ligand based gene transfer in vivo.
>
> In response, the references have been considered but do not overcome the art recognized problems previously and repeatedly indicated. Shortcomings in gene therapy approaches include the unpredictability in providing adequate quantities of nucleic acid therapeutics by delivery specifically to desired target cells in a subject, unpredictability in reaching a desired subcellular target site, e.g., in the cytoplasm or nucleus and the ability to find and bind the target

> site and simultaneously avoid nonspecific binding (see, e.g., Branch and Ma).
>
> The claims are very broad. They are drawn to the ability to successfully and predictably deliver an expansive genus of compounds to any target cell in vitro or in an organism. The ability to deliver adequate quantities of nucleic acids or therapeutic molecules to any target cell in an organism remains a highly unpredictable endeavor.

Applicants respectfully disagree. With respect to assertions made in the Office Action regarding shortcomings in gene therapy, Applicants note that the Office Action is not disputing whether the invention allows introduction of nucleic acids into cells but rather questioning the extent that this takes place and applying a qualitative assessment. However, it should be pointed out that the claims as written only state: "a method of introducing a nucleic acid component into a cell……" As such, there is no language in the claims that stipulates "with high efficiency" or any other expressions denoting the level of expression achieved by the claimed methods. In point of fact, if only a single nucleic acid is introduced into a single cell in vivo the steps set forth in claim 262 would have been accomplished. In Applicant's view, the level of expression that can be achieved is an application of optimization, processes rather than the inventive concepts themselves. The process would only reflect a claim if it read: "A method of procuring a therapeutic effect by introducing a nucleic acid component into a cell….."

Applicants note that it is well established case law that the enablement requirement is met if the description enables any mode of making and using the invention. *Invitrogen Corp. v. Clontech Laboratories, Inc.* 429 F.3d 1052 (CAFC 2005). It is actually conceded in the Office Action that *in vitro* methods are indeed enabled. Thus, given that at the very least *in vitro* methods are enabled, claim 263 would be enabled as well. Further, as asserted in previous responses to the Office Action, the specification in combination with teachings of the art, Applicants assert that the claimed method would be enabling *in vivo* as well. Specifically, various domain with specific cell binding properties are disclosed in the specification on page 53, lines 10-18. Further, methods for the *in vivo*

administration were well known in the art as of the priority date of the above-referenced application. One of the prior art references cited in the instant Office Action, Meyer, has an extensive discussion of ligand mediated transport of ODNs in columns 4-6. "Systemic administration" is described in the passages of column 19 lines 38 to column 20, line 25 of Meyer as well.

Applicants assert that as noted above, claim 264, directed to an *in vivo* method would be enabled by the specification. Further, claim 265 directed to an ex vivo method is enabled as well in view of the above arguments and the Examiner's assertions.

In view of the above arguments, Applicants assert that the rejections under 35 USC §112, first paragraph (enablement) has been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

3. **The Rejections Under 35 U.S.C. §102(e) (Meyer)**

Claims 245-255, 257-260, 262, and 306 have been rejected under 35 U.S.C. §102(e) as being anticipated by Meyer et al. (U.S. Patent 5,574,142), for the reasons of record set forth in the Office Action mailed 2-25-08 and as set forth below. The Office Action specifically states:

> Contrary to Applicant's assertions, Meyer is not limited to teaching antisense ODNs as part of the cell delivery compounds. Rather, Meyer teaches an array of components that are contemplated as being components of the cell delivery systems as instantly claimed. They include ribozymes, which comprise domains to a specific nucleic acid component (the non-binding domains of the ribozyme) and a specific nucleic acid (the target binding domain of the ribozyme), as well as including triplex DNA optionally comprising alkylating groups, cleaving groups or other functional groups, which comprise domains to a specific nucleic acid component (the non-target binding strands, or functional groups, as well as the specific nucleic acid component (the target binding domain). Furthermore, it is noted that the domain of a nucleic acid that is involved in being covalently or non-covalently linked to either the targeting ligand or peptide domain of the cell delivery system taught by

> Meyer is not necessarily the domain that participates in target binding, once delivered to the target molecule, since this portion or domain to the nucleic acid would not have target binding capacity, due to its chemical modification, also qualifying this derivatized portion of oligonucleotides as a domain to the nucleic acid, but not the specific nucleic acid domain.

Applicants respectfully traverse the rejection. It is Applicants' assertion that Meyer does not contain all of the elements of the pending claims. First, claim 245, as amended recites that the nucleic acid construct directs synthesis of a nucleic acid product, said comprises a sequence hybridized to a complementary polynucleotide sequence of a linear polynucleotide tail wherein said polynucleotide tail is covalently attached to an antibody. Meyer provides no teaching of a construct that directs synthesis of a nucleic acid product. The anti-sense ODNs, ribozymes or triplex DNA would actually result in degradation of the template DNA. Second, claim 245 specifically recites that a polynucleotide tail is covalently attached to an antibody. In contrast, in Meyer, a peptide is attached to an antibody (see Figure 4). Claim 246 depends from claim 245. Thus, arguments made with respect to claim 245 would apply to claim 246.

Similarly, claims 247 and 306 as amended would not be anticipated by Meyer. This is because as noted above, none of the constructs taught in Meyer would direct synthesis of a nucleic acid product. The oligonucleotides in the conjugates of Meyer as noted in the abstract are "capable of selectively binding to a target sequence of DNA, RNA or protein inside a target cell". Claims 248, 251 and 262 ultimately depend from claim 247. Thus, arguments made with respect to claim 247 would apply to these claims as well. Claims 249-250 and 253-255 and 257-260 have been canceled.

In view of the above arguments, the amendments of claims 245, 247 and 306, the cancellation of claims 249-250 and 253-255 and 257-260, Applicants assert that the rejection under 35 U.S.C. §102(e) over Meyer et al. has been overcome. Therefore, Applicants respectfully request that the rejections under 35 U.S.C. §102(e) over Meyer et al. be withdrawn.

**4. Objection to Claim 247**

Claim 247 is objected to because of the following informalities:

> The claim appears to be grammatically incorrect, see esp. lines 4-5. The "and" has been deleted in line 4, so it is unclear what the relationship is between what is listed in (a) relative to (b) of the claim.

In response, as noted above, claim 247 has been amended. This claim amendment does include "and" between recitation of (a) and (b). Therefore, the objection has been overcome and should be withdrawn.

**5. The Rejection Under 35 USC §112, Second Paragraph**

Claims 249, 250, 257 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In response, Applicants note that claim 249, 250 and 257 have been canceled in order to advance prosecution. Applicants do reserve the right to file subsequent continuation and/or divisional applications on the canceled subject matter. In view of the cancellation of claims 249, 250 and 257, the rejection under 35 USC §112, second paragraph has been overcome and should be withdrawn.

**6. The Rejection Under 35 USC §102(e)**

Claims 245-255,257-265, and 306 are rejected under 35 U.S.C. 102(e) as being anticipated by Curiel et al. (U.S. Patent 5,521,291). The Office Action specifically states:

> Curiel et al. (U.S. Patent 5,521,291) teach methods, compositions, target cells for delivering compositions to cells in vitro and in vivo, and kits for target cell delivery, which compositions comprise a construct having at least one terminus comprising a polynucleotide tail hybridized to a complementary polynucleotide and an antibody bound to the hybridized polynucleotide (e.g. ribozymes attached to antibodies, or viral nucleic acids for target cell delivery in combination with antisense for target gene inhibition, target cell ligands), which constructs are

> optionally bound non-ionically to a ligand, and compositions which optionally comprise a domain to a specific nucleic acid component and a domain to a cell of interest, and a different, specific nucleic acid desired to be delivered to said cell, and optionally comprising a binder which is optionally the same as the domain to a cell of interest, or a polylysine, or one which mediates ligand binding to a receptor, including lectins, antigens and other receptors (see esp. the abstract; Fig. 1; col. 3-11; 13; 16; example 6, col. 24-29; claims 3, 5, 6,14 and 15).

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claims 245, 247 and 306 have been amended to more distinctly recite the subject matter that Applicants regard as their invention. Specifically, as noted above, claim 245 as amended is directed to a nucleic acid construct that directs synthesis of a nucleic acid product and comprises a sequence hybridized to a complementary polynucleotide sequence of a linear polynucleotide tail wherein said polynucleotide tail **is covalently attached** to an antibody. In contrast, Curiel et al., do not describe any covalent linkages between an antibody and a nucleic acid as required by claim 245. Claim 246 depends from claim 245. Thus, arguments made with respect to claim 245 would apply to claim 246 as well.

Applicants further note that claims 247 and 306 as amended recites that the domain to a specific nucleic acid component may be a linear nucleic acid complementary to a sequence of the specific nucleic acid component or a protein that binds to a ligand of a modified nucleotide in the specific nucleic acid component. In contrast, Curiel et al., use polylysine for binding a nucleic acid into a complex, a component that is not recited as one of the possible domains to a nucleic acid in claim 247. Further, even if one were to broadly interpret one of the strands of the plasmid in Curiel to be a (i) domain to a nucleic acid, it is part of a circular plasmid and would not be considered to be linear.

Claims 248, 251, 253, 263-265 depend from claim 247. Therefore, arguments made with respect to claim 247 would apply to these claims as well. Applicants further note that claims 249-250, 254-255 and 257-260 have been canceled.

In view of the above amendments and arguments, Applicants assert that the rejections under 35 USC §102(e) (Curiel) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

**7. Double Patenting**

Claims 245-255, 257-260, 262-265 and 306 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 275, 289, 290, 296-301 of copending application No. 08/978,634. Further, claims 245-255, 257-260, 262, and 306 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of copending Application No. 11/929,897.

Applicants will address the Provisional Double Patenting Rejections once there is indication of allowable subject matter.

**8. Conclusion**

Applicants assert that the claims are in condition for allowance. If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at (914) 712-0093.

Respectfully submitted,

/Cheryl H Agris/

Dated: March 25, 2009 Cheryl H. Agris, Reg. No. 34,086